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Prolonged Antihistaminic Therapy: Effects of a 7-day Administration of Loratadine on Vigilance and Alertness

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Titel	: Meerdaagse antihistaminicum-therapie: effecten van een 7-daags gebruik van loratadine op vigilantie en alertheid
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Antihistaminica worden voorgeschreven door huisartsen, longartsen, KNO-artsen en dermatologen voor een verscheidenheid aan allergische aandoeningen van onderste en bovenste luchtwegen en van de huid. In een eerder verrichte studie, uitgevoerd in opdracht van de Directie Militair Geneeskundig Beleid en het Centraal Militair Hospitaal, is vastgesteld dat een eenmalige dosering van 10 mg loratadine geen nadelige effecten heeft op de prestatie tijdens het uitvoeren van 'flying ability' taken gedurende een periode van 1-6 uur na inname (Valk & Simons, 1995; Valk, Simons, Struyvenberg, Kruit & Van Berge Henegouwen, 1997). Aangezien in de dagelijkse praktijk loratadine vaker wordt voorgeschreven voor een langere periode, werd een vervolgstudie uitgevoerd om het mogelijk vóórkomen van sedatieve effecten als gevolg van een meerdaagse toediening van loratadine na te gaan.

Op het Nationaal Lucht- en Ruimtevaartgeneeskundig Centrum werd bij 19 mannelijke proefpersonen loratadine 10 mg vergeleken met placebo bij een eenmaal daagse toediening gedurende 7 dagen. Om eventuele interacties met milde hypoxie te kunnen bepalen, werd het onderzoek uitgevoerd in de hypobare kamer van het NLRGC. Metingen werden verricht op zeeniveau en op 8000 ft (75.2 kPa, overeenkomend met standaard cabinedruk). De prestaties werden bepaald met behulp van objectieve (vigilantie en tracking) en subjectieve (slaperigheid) tests.

Gedurende de behandelingsperiode werden in beide omgevingscondities geen significante verschillen in testprestatie gevonden tussen loratadine en placebo. Hieruit werd geconcludeerd dat verwacht mag worden dat loratadine geen sederende bijwerking heeft en de vliegprestatie niet nadelig beïnvloedt wanneer het gedurende 7 dagen volgens de aanbevolen therapeutische dosering (1 d.d. 10 mg) wordt gebruikt. Op grond van de resultaten van deze studie en het farmaco-kinetisch profiel wordt verondersteld dat prestaties niet nadelig zullen worden beïnvloedt wanneer loratadine langer dan 7 dagen wordt gebruikt. De conclusies van de huidige studie zijn tevens van toepassing bij de behandeling van personeel werkzaam in functies met vergelijkbare taakomstandigheden, zoals luchtverkeersleiders, duikers en tank-bestuurders.

Prolonged antihistaminic therapy: effects of a 7-day administration of loratadine on vigilance and alertness

P.J.L. Valk, M. Simons, T. Meeuwsen

Abstract

In an earlier study, commissioned by the Director of the Military Medical Policy and the Central Military Hospital, it was found that a single dose of 10 mg loratadine did not affect performance on flying ability tasks during a time period of 1-6 hours after ingestion. In daily practice loratadine will often be prescribed for an extended period. To rule out sedative effects of loratadine during such a prolonged treatment, this study was conducted. In a randomised, double-blind, placebo controlled, 'within-subjects' design, 19 male subjects were studied. Loratadine 10 mg and placebo were administered once daily during 7 days. Objective (vigilance and tracking) and subjective (alertness) tests, tailored to the specific tasks of aircrew, were applied to assess performance. To determine possible interaction effects with mild hypoxia, measurements were performed in a hypobaric chamber at sea level and at 8000 ft (75.2 kPa, standard cabin pressure). In either environmental condition, the results of this study did not reveal significant differences between loratadine and placebo treatments. It is anticipated that loratadine is free of sedative effects and does not affect performance when it is given for 7 days in the recommended therapeutic dose.

Meerdaagse antihistaminicum-therapie: effecten van een 7-daags gebruik van loratadine op vigilantie en alertheid

P.J.L. Valk, M. Simons, T. Meeuwsen

Samenvatting

In een eerder verrichte studie, uitgevoerd in opdracht van de Directie Militair Geneeskundig Beleid en het Centraal Militair Hospitaal, is vastgesteld dat een eenmalige dosering van loratadine 10 mg de prestatie op 'flying ability' taken gedurende een periode van 1-6 uur na inname niet nadelig beïnvloedt. In de dagelijkse praktijk zal loratadine vaker worden voorgeschreven voor een langere periode. De onderhavige studie is uitgevoerd om sedatie als gevolg van een meerdaagse toediening van loratadine uit te sluiten. In een gerandomiseerd, dubbel blind, placebo gecontroleerd, 'within-subjects' design, zijn 19 mannelijke proefpersonen onderzocht. Loratadine 10 mg en placebo werden daarbij eenmaal daags gedurende 7 dagen toegediend. Objectieve (vigilantie en tracking) en subjectieve (slaperigheid) tests, toegesneden op de specifieke taken van vliegers, werden gebruikt om de prestatie te meten. Om eventuele interactie-effecten met milde hypoxie te bepalen, werden de metingen in een hypobare kamer verricht op zeeniveau en op 8000 ft (75.2 kPa, standaard cabinedruk). In beide omgevingscondities werden geen significante verschillen gevonden tussen loratadine en placebo. Geconcludeerd werd dat verwacht mag worden dat loratadine geen sederende bijwerking heeft en de vliegprestatie niet nadelig beïnvloedt wanneer het gedurende 7 dagen volgens de aanbevolen therapeutische dosering wordt gebruikt.

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1 INTRODUCTION

In an earlier study, commissioned by the Director of the Military Policy and the Central Military Hospital, it was found that in situations where pilots have to remain vigilant, performance was affected by the sedative effect of antihistamines, such as triprolidine hydrochloride 5 mg. A single dose of 10 mg loratadine showed no performance decrements on flying ability tasks during a time period of 1-6 hours after ingestion (Valk & Simons, 1995; Valk, Simons, Struyvenberg, Kruit & Van Berge Henegouwen, 1997). Based on the results of this study it was concluded that there was no longer need to ground pilots treated with a single dose of 10 mg loratadine. This conclusion is also relevant for other highly skilled professions requiring optimal vigilance and alertness (Army, Navy, ground crew Air Force).

In daily practice loratadine will often be prescribed for an extended period. Therefore, it is necessary to rule out sedative effects of loratadine during such a prolonged treatment. Results of earlier studies indicate that, when investigating sedative effects of antihistamines, possible detrimental effects can best be demonstrated by tasks addressing vigilance and/or tracking performance (Valk et al., 1997; Simons, Valk & Cornelissen, 1988). These tasks incorporate a low level of workload and appear to be most sensitive to demonstrate performance decrement on alertness function and sustained attention due to the intake of sedative compounds. In contrast, complex tasks are characterized by a high level of workload, which increases the level of arousal and therefore masks possible sedative effects.

In order to investigate these relevant issues, the present study has been designed to assess the time response on vigilance and tracking performance, and alertness in healthy volunteers following a 7-day treatment with loratadine 10 mg, administered once daily, and placebo. The decision to investigate a treatment period of 7 days was based on the pharmaco-kinetic profile, that evidences steady state levels of loratadine and its metabolite (descarboethoxyloratadine) after 5 days (Radwanski, Hilbert, Symchowicz & Zampaglione, 1987). Effects of antihistamines on performance might be aggravated by the hypobaric hypoxic effects of the cockpit environment (Simons, 1990). Therefore, measurements were performed under hypobaric conditions and at sea level.

2 METHOD

2.1 Subjects

Twenty healthy male volunteers were selected to participate in this study. Because of personal reasons, one of them had to be withdrawn just before the start of the experiment and could not be replaced. The remaining nineteen were nonsmoker and drug free from 3 months prior to the study. Age ranged from 19-33 years (mean: 25.0 yrs), weight from 64-92 kg (mean: 76.5 kg), and height from 170-194 cm (mean: 180.8 cm). All medical examination parameters, including liver functions, were within normal range. Written informed consent of each volunteer was obtained after a full explanation of the nature of the study. Subjects were paid for participation, and all completed the study. The protocol of the study was approved by the medical ethical committee of the Central Military Hospital.

2.2 Assessment methods

In earlier studies, sensitivity of the Vigilance and Tracking task (VigTrack; Valk, 1994) for sedative effects of antihistamines has been established (Valk & Simons, 1995). Thus, the use of a positive control, such as triprolidine hydrochloride, was considered to be redundant. This previous study also showed that complex tasks increased the level of arousal, and masked possible sedative effects. Therefore, in the present study only the VigTrack was used.

The Stanford Sleepiness Scale (SSS: Hoddes, Zarcone, Smythe, Phillips & Dement, 1973) was used to assess subjective ratings on alertness. Both, VigTrack and SSS were performed on a Psion-3a palm top computer.

Subjective adverse reactions were determined by using an indirect technique (i.e. asking 'How do you feel') throughout the study. Recently two cases of subfulminant liver failure and severe hepatotoxicity have been attributed to loratadine use (Schiano, Bellary, Cassidy, Thomas & Black, 1996). Although evidence for loratadine being the only causal factor in both cases was not convincing, it was decided to monitor blood levels of alkaline phosphatase and γ-glutamyl transferase at the pre-trial medical examination, and on the fifth and seventh treatment day during both treatment periods as an objective measure of this potential adverse reaction. Blood was collected by venapuncture of the ante-cubital vein.

2.2.1 Vigilance and Tracking (VigTrack)

The VigTrack task (Fig. 1) is a dual-task measuring vigilance performance under the continuous load of a compensatory tracking task. The task has been developed on a Psion 3a palmtop computer and is successfully applied in field studies concerning effects of fatigue and sleepiness in pilots (Valk &

Simons, 1996; Simons & Valk, 1997). During the tracking task, subjects have to steer a cursor-block so that it is kept between two markers. The cursor-block is programmed to move continuously from the two markers in the centre of the display. Using arrow-keys on the computer keypad, the subject has to keep the cursor-block between these two markers by compensatory tracking. While tracking, subjects have to perform the vigilance task. During this task a moving dot leaps between two horizontal lines on top of the computer screen. Most of these leaps are equidistant. However, some of them are twice the normal size. If the latter is the case, subjects have to respond as quickly as possible by pressing a response button. The duration of this test was 10 minutes and performance measures included root mean square tracking error, percentage omissions and number of false reactions.

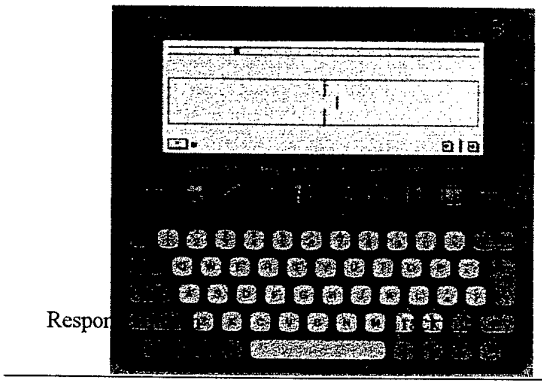

Fig. 1: Psion 3a: Vigilance and Tracking task (VigTrack)

2.2.2 Subjective assessment of alertness (SSS)

The Stanford Sleepiness Scale (Table 1) was used to subjectively assess the sedative effects of the different compounds. This subjective rating scale has proven to be very sensitive in detecting any significant increase in sleepiness or fatigue. Furthermore SSS measures showed to be highly correlated with flying performance and threshold of information processing speed during periods of intense fatigue (Perelli, 1980).

Table 1: Stanford Sleepiness Scale (SSS)

1. Feeling active and vital; alert; wide awake.
2. Functioning at a high level, but not at peak; able to concentrate.
3. Relaxed; awake; not at full alertness; responsive.
4. A little foggy; not at peak; let down.
5. Foggy; beginning to lose interest in remaining awake; slowed down.
6. Sleepy; prefer to be lying down; fighting sleep; woozy (NL: suf).
7. Almost in reverie; sleep onset soon; losing struggle to remain awake.

2.2.3 Peripheral haemoglobin-oxygen saturation (SaO_2)

Throughout their stay in the hypobaric chamber, SaO_2 of each subject was determined, using a pulse oximeter with finger clip sensor (Nonin Medical Inc.). Recording was performed to control both experimental conditions on SaO_2 values and to demonstrate subjects' SaO_2 values to be in agreement with values normally found under these hypobaric conditions. This non-invasive technique is routinely used in hypobaric tests at the Netherlands Aerospace Medical Centre, where it was shown that SaO_2 ranged from 89-93% in large groups of subjects staying at a simulated altitude of 8000 ft (Simons, 1990).

2.3 Design and treatments

A randomised (sequentially balanced Latin square), double-blind crossover ('within-subjects') design was used, employing loratadine 10 mg (Claritine^R), and placebo. The sequence of the two environmental conditions was fixed during the entire experiment (i.e. sea level followed by 8000 ft). Both compounds were supplied by Schering-Plough BV, and randomization, blinding, and matching were carried out by the department of pharmacy of the Anthonius Hospital, Nieuwegein. The test substances were administered for a 7-day period in a once daily oral dose. Between the treatment periods there was a wash out period of 7 days.

2.4 Procedure

A schematic overview of the test procedure is presented in Table 2. Complete medical examination of the volunteers was performed 7 days before the first test day. On the same day, participants were familiarized to the test procedure and were trained on the performance test. During treatment weeks, subjects took their medication daily at 10:30 hr and test sessions were performed on day 1,5, and 7, including VigTrack, subjective assessment of alertness, and SaO_2 measurement.

Table 2: experimental schedule treatment week

Treatment Day	Time	Experimental Condition	Test Session	Action
1,5,7	10:30			arrival / medical evaluation / drug administration
	10:45	sea level	1	
	11:00			pressure decrease (8000 ft, 75.2 kPa)
	11:10	hypoxia	2	
	11:25			pressure increase (sea level)
	11:35			medical evaluation / return home
2,3,4,6	10:30			drug administration

On day 1,5, and 7, subjects arrived at the research laboratory at 10.30 hours and underwent a brief medical evaluation. At 10.45 the first test session (VigTrack, SSS, SaO_2) was performed at sea level. Thereafter, ambient pressure was decreased to 75.2 kPa and at 11.10 hours a second test session was performed. At the end of this session, ambient pressure was increased to sea level value, and subjects returned home after a brief medical evaluation. At the start of the study and at the end of the treatment days 5 and 7 of each treatment period, a venous blood sample was taken.

2.5 Data analysis

All VigTrack variables that were repeatedly measured were tested in separate applications of a 2 x 3 x 2 repeated measures analysis of variance (treatment, test day, environmental condition). SSS-scores were analysed by non-parametric statistics (Wilcoxon Matched-Pairs Signed-Rank test).

3 RESULTS

3.1 Vigilance and Tracking (VigTrack)

The percentage omitted targets (Fig. 2a) on the VigTrack task showed to be stable during treatment weeks. No significant differences were found between the loratadine and placebo condition. Scores on this parameter tended to be better at sea level as compared to 8000 ft ($F(1,18)=3.61$, $p<.074$).

Tracking performance on this same task (Fig. 2b) improved significantly during treatment weeks for both the loratadine and the placebo group($F(2,36)=6.71$, $p<.003$). No significant differences were observed between treatment conditions.

With respect of the third parameter of this task, the number of false reactions (Fig. 2c) did not significantly differ between the two groups. Subjects made significantly more false reactions at sea level as compared to 8000 ft ($F(1,18)=7.73$, $p<.012$).

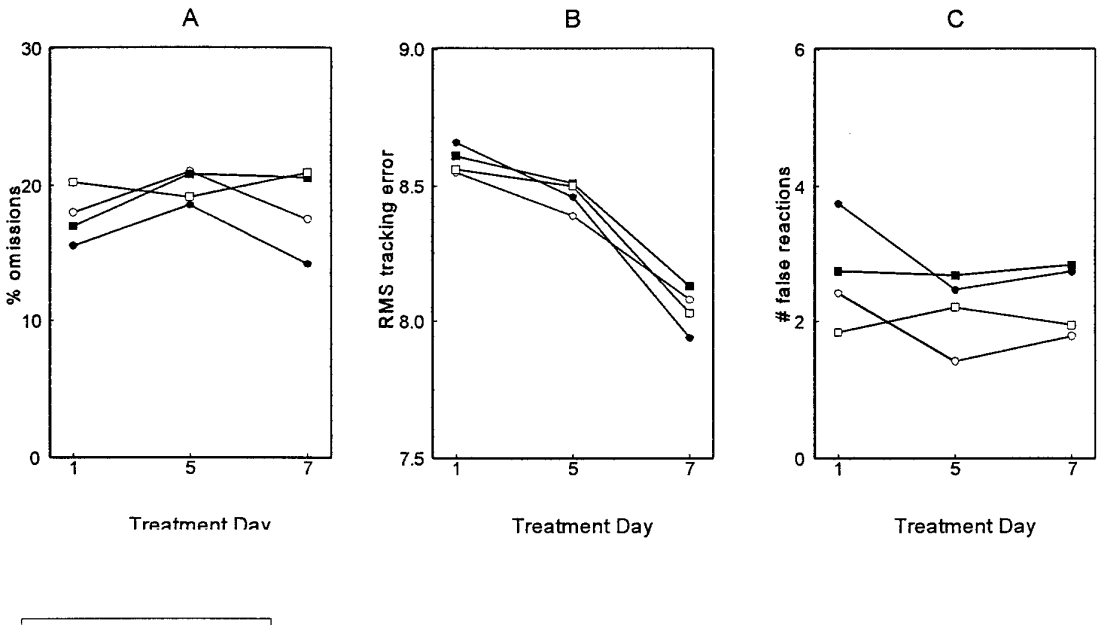

Fig. 2: Mean VigTrack performance (a-c) on day 1, 5, and 7 of the treatment periods. Mean % omissions (a), mean tracking RMS (b), and mean number of false reactions are presented for the loratadine and placebo treatment at sea level and at 8000 ft.

3.2 Alertness (SSS)

Mean subjective scores on alertness, as measured by the Stanford Sleepiness Scale are presented in Fig. 3. No significant overall effects were found with respect of treatment conditions. However, mean ratings for the loratadine group tended to be increased on the fifth treatment day, indicating a decreased alertness ($Z=-1.42$, $p<.075$). When differentiating between sea level and 8000 ft conditions, this effect reached the level of significance at 8000 ft ($Z=-1.68$, $p<.046$). On the last day of the treatment period this effect could not be demonstrated.

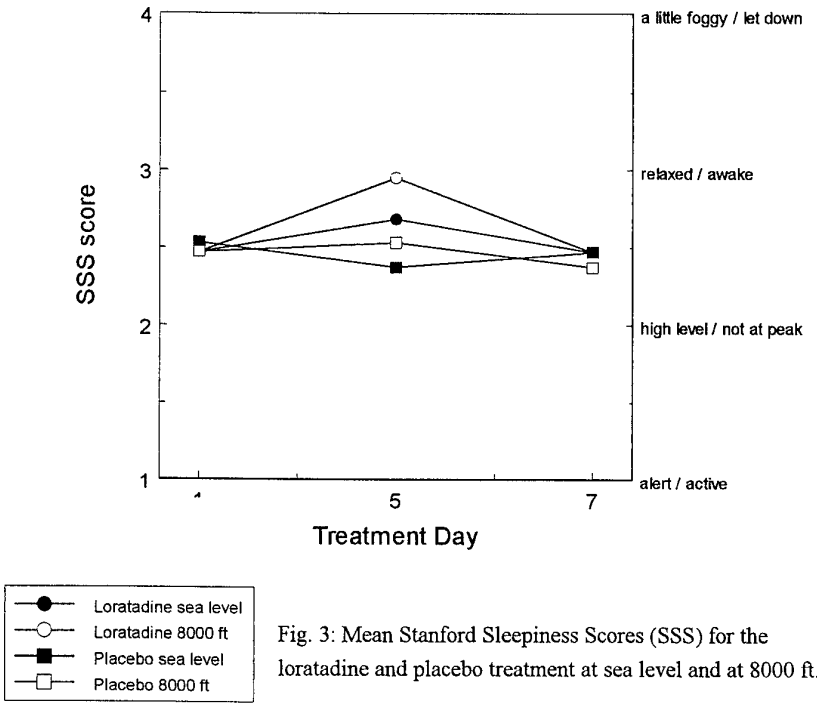

Fig. 3: Mean Stanford Sleepiness Scores (SSS) for the loratadine and placebo treatment at sea level and at 8000 ft.

3.3 Haemoglobin-oxygen saturation (SaO_2)

Mean SaO_2 values did not show significant differences between the experimental conditions. Mean baseline values on test days ranged from 98.1% to 98.3%. At 8000 ft, SaO_2 decreased to 92.2%, 92.6%, and 92.0% on the 1st, 5th, and 7th treatment day respectively.

3.4 Adverse reactions

One case of a frontal headache was recorded on the fifth trial day. Because the headache subsided spontaneously after three hours, the subject completed the study, while it was not necessary to break the subject's code. Throughout the study, blood levels of alkaline phosphatase and γ-glutamyl transferase of each subject were within normal range (AP: 38-126 u/l; γGT: 8-78 u/l).

4 DISCUSSION AND CONCLUSION

The aim of this study was to investigate possible sedative effects of a 7-day treatment with loratadine 10 mg, administered once daily, on vigilance and tracking performance, and alertness. To examine possible interaction effects with the cockpit environment, treatments were evaluated at sea level and under the condition of simulated cabin altitude (8000 ft). In either environmental condition, the results of this study did not reveal significant performance differences between loratadine and placebo treatments. Subjective alertness for the loratadine group tended to be decreased on the fifth treatment day, but this effect was not observed on the first and seventh day.

All performance parameters of the Vigilance and Tracking task showed no significant differences between loratadine and placebo. During treatment periods, the percentage omissions varied from 17.5% to 19.8% in the loratadine and placebo group respectively. These figures are slightly better as compared to those of the single dose study (Valk et al., 1997). Similar results were found for the overall mean of the tracking component. In contrast to the single dose study, where measurements were repeated 5 times during one trial day, tracking performance in this study improved significantly during treatment weeks for both treatment conditions. Mean tracking performance on the last treatment day was about 7% better as compared to the first treatment day.

Some researchers suggest that possible sedative effects of 'non-sedating' antihistamines can be masked when test parameters are based on overall sum or mean test scores (O'Hanlon, 1997). Therefore, they suggest dividing raw data of each individual test session into equal time intervals. Recalculating sum or mean scores for each time interval results in performance profiles over time. Analysing this so called 'time on task' performance could reveal possible sedative effects. Following these premises, raw data of the 10-minutes tests were divided into 5 intervals of 2 minutes each (Fig. 4). Looking closer into the data, we could not demonstrate 'time on task' effects, as illustrated in the two representative examples. Both the loratadine and the placebo group showed comparable performance profiles; performance is best during the first minutes of the task. Thereafter, performance impairs over time and is worst at the end of the 10-minute task.

Alertness for the loratadine group, as measured by the Stanford Sleepiness Scale, tended to be slightly decreased on the fifth treatment day as compared to placebo. When differentiating between sea level and 8000 ft environmental conditions, this effect became significant at 8000 ft. However, on the first and seventh treatment day, no such an effect could be demonstrated. A possible explanation for this finding might be the report of a frontal headache by one of the subjects who was treated with loratadine on this fifth trial day. This complaint might have influenced his subjective rating of alertness. Reanalysing the data, excluding this specific subject, resulted in the elimination of the significant difference between the loratadine and placebo group.

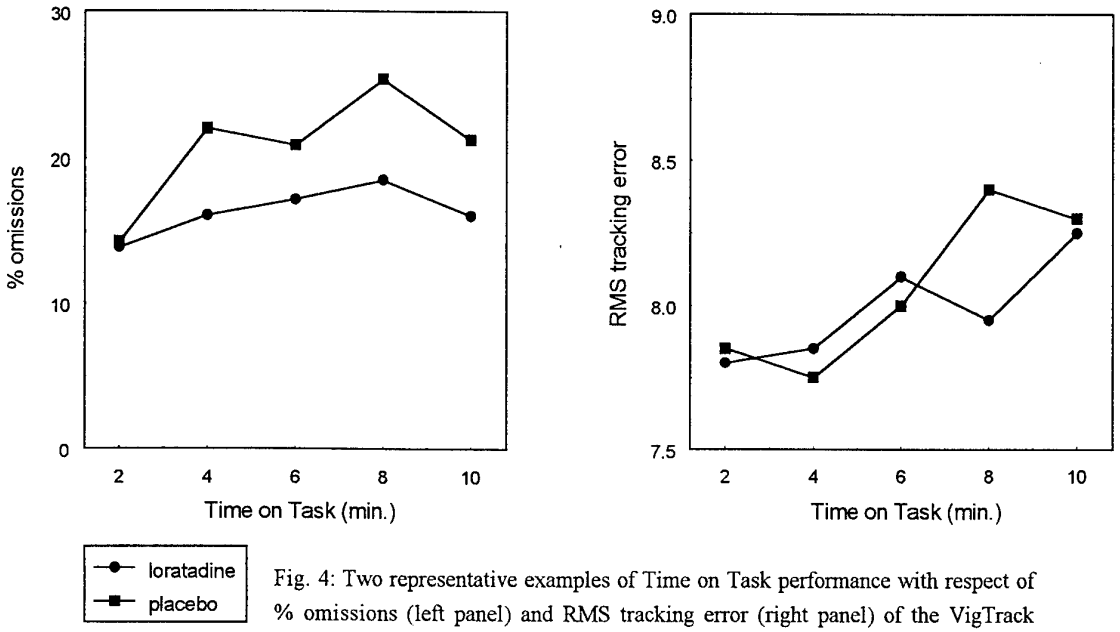

Fig. 4: Two representative examples of Time on Task performance with respect of % omissions (left panel) and RMS tracking error (right panel) of the VigTrack task. Figures are combined scores from sea level and 8000 ft on the 7th treatment day for the loratadine and placebo condition.

No studies were found where the effects on performance were investigated for a prolonged period of 7 days using loratadine in the recommended therapeutic dose. Multiple dose studies showed a significant impairing effect on performance when loratadine was given over 4 days in twice the therapeutic dose (i.e. 20 mg; Riedel, Ramaekers, Uiterwijk & O'Hanlon, 1990). This effect could not be demonstrated when applying loratadine 10 mg once daily, during a 4-day period (Riedel, Schoenmakers & O'Hanlon, 1989). Therefore, some researchers suggest that, when finding significantly impaired performance due to multiple, supra-therapeutic dosage, there is at least an indication that normal doses might be able to impair performance in a small fraction of the total user population (O'Hanlon & Ramaekers, 1995). Although this statement is theoretically and statistically correct, it is hard to prove in laboratory studies.

Based on the absence of sedative effects during a 7-day treatment with loratadine 10 mg and based on the multiple-dose pharmacokinetics of loratadine and its active metabolite descarboethoxy-loratadine (Radwanski et al., 1987), it can be assumed that performance will not be affected when loratadine is used for periods exceeding one week.

It is good clinical practice that pilots suffering from allergic rhinitis or other allergic diseases who are treated with loratadine, are monitored carefully not only because of this medication. It remains necessary for the physician to determine the antihistamine's desired effect, and to decide, on an individual basis, whether the pilot is physically and mentally fit to fly. To do so, it is recommended to develop 'Fitness to Fly' and 'Fitness for Duty' assessment tools that can support the physician to take a well-considered decision in individual cases.

Conclusion

Based on the results of this study, we conclude that loratadine is free of sedative effects and does not affect performance when it is given for 7 days in the recommended therapeutic dose. Therefore, there is no need to ground pilots when treated with loratadine 10 mg, administered once daily for an extended period (7 days). The flight surgeon should determine the antihistamine's desired effect, and decide, on an individual basis, whether the pilot is physically and mentally fit to fly. The conclusions of the present study also apply for the treatment of operators of other highly skilled tasks, such as air traffic controllers, divers, and tank drivers.

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14. SUPPLEMENTARY NOTES

15. ABSTRACT (MAXIMUM 200 WORDS, 1044 BYTE)

In an earlier study, commissioned by the Director of the Military Policy and the Central Military Hospital, it was found that a single dose of 10 mg loratadine did not affect performance on flying ability tasks during a time period of 1-6 hours after ingestion. In daily practice loratadine will often be prescribed for an extended period. To rule out sedative effects of loratadine during such a prolonged treatment, this study was conducted. In a randomised, double-blind, placebo controlled, 'within-subjects' design, 19 male subjects were studied. Loratadine 10 mg and placebo were administered once daily during 7 days. Objective (vigilance and tracking) and subjective (alertness) tests, tailored to the specific tasks of aircrew, were applied to assess performance. To determine possible interaction effects with mild hypoxia, measurements were performed in a hypobaric chamber at sea level and at 8000 ft (75.2 kPa, standard cabin pressure). In either environmental condition, the results of this study did not reveal significant differences between loratadine and placebo treatments. It is anticipated that loratadine is free of sedative effects and does not affect performance when it is given for 7 days in the recommended therapeutic dose.

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